Treatment of brain metastases in patients with driver mutations: WBRT, SRS or systemic treatment only?

Laurie E Gaspar MD MBA
Professor, Radiation Oncology
University of Colorado, USA
Disclosures

• None

Acknowledgements

• Jonathan Khalifa MD
• Arya Amini MD
• Sanjay Popat MD
• Corinne Faivre-Finn MD
• Paul Sperduto MD
• Paul Brown MD
Congratulations Laurie, you achieved top stats in March

Your research is in the spotlight

With 25 new citations, you were the most cited researcher from the Dominican Republic in March

Go to your stats
## Graded Prognostic Assessment (GPA)
### Lung (NSCL and SCLC)

<table>
<thead>
<tr>
<th>PF</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>Pt. Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>50-60</td>
<td>&lt;50</td>
<td>________</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70-80</td>
<td>90-100</td>
<td>________</td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td>Absent</td>
<td></td>
<td>________</td>
</tr>
<tr>
<td>#BM</td>
<td>&gt;3</td>
<td>2-3</td>
<td>1</td>
<td>________</td>
</tr>
</tbody>
</table>

Sum Total = ________

Sperduto PW et al. JCO 2012;30:419-425
www.brainmetgpa.com
### Graded Prognostic Assessment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>GPA 0-1.0</th>
<th>GPA 1.5-2.0</th>
<th>GPA 2.5-3.0</th>
<th>GPA 3.5-4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC/SCLC</td>
<td>3.0</td>
<td>5.5</td>
<td>9.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.4</td>
<td>4.7</td>
<td>8.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>3.4</td>
<td>7.7</td>
<td>15.1</td>
<td>25.3</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>3.3</td>
<td>7.3</td>
<td>11.3</td>
<td>14.8</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3.1</td>
<td>4.4</td>
<td>6.9</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Sperduto PW et al. JCO 2012;30:419-425
www.brainmetgpa.com
Survival of NSCLC Patients with Brain Metastases: Comparison of Current Data to Historical Controls

- **2006-2014 cohort**
  - $n = 2186$
  - MST = 12.3 months

- **1985-2005 cohort**
  - $n = 1833$
  - MST = 7.1 months
Patient Population

2324 patients with lung cancer
  → 2186 with non-small cell lung cancer
    → 1521 with adenocarcinoma
      → 993 with known mutation status

Largest reported series of gene mutations in patients with lung adenocarcinoma and brain metastases
Survival by ALK Mutation Status

Proportion surviving

Months from start of BM treatment

ALK+
- n = 90
MST = 45 mo.

ALK-
- n = 535
MST = 16 mo.
Survival by KRAS Mutation Status

KRAS -
n = 497
MST = 19 mo.

KRAS +
n = 217
MST = 12 mo.

Months from start of BM treatment
Cause of Death

In the 512 patients (34%) in which cause of death was known, 82% died from non-CNS disease, suggesting…

• Systemic disease remains the primary obstacle to further progress.
• Local failure rate after SRS for BM is roughly 20% and those pts are likely to die from CNS progression.
Brain/LM metastases is a common site of first progression in EGFRmut and ALK+ patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Clinical Data</th>
<th>% Brain/LM progression</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amuro AM, Cancer 2005</td>
<td>EGFRmut+/- who responded to gefitinib</td>
<td>33% (first site)</td>
<td>15m survival after dx of BM/LM</td>
</tr>
<tr>
<td>Heon S, Clin Cancer Res 2010</td>
<td>EGFRmut+ on gefitinib or erlotinib</td>
<td>29% crude; 19% at 2 years, cumulative</td>
<td>5-6 m survival after prog/dx of BM/LM</td>
</tr>
<tr>
<td>Shaw AT, Lancet Oncol 2011</td>
<td>ALK+ on crizotinib</td>
<td>50% cumulative</td>
<td></td>
</tr>
<tr>
<td>Costa DB, J Clin Oncol 2015</td>
<td>ALK+ on crizotinib</td>
<td>20% if no prior BM, 38% if prior BM</td>
<td>BM responses seen. PFS similar in patients with/without BM at study entry</td>
</tr>
</tbody>
</table>
Cumulative incidence of CNS progression in EGFRmut+ on gefitinib or erlotinib

Increased risk of new brain metastases if prior brain metastases
NO574 SRS ± WBRT
65% NSCLC

1-3 brain mets appropriate for SRS

ECOG PS 0-2

No LM

No chemo during RT

• Institution
• 1 vs 2-3 lesions
• Extracranial tumor control
• Age

Primary Endpoint: 3 month neurocognitive change

Accrual: 214 patients 2002-2013
**N0574 Brain Control vs. ARM**

- **Cumulative Incidence %**
  - SRS
  - SRS+WBRT

- **p < 0.0001**

**N0574 OS vs. ARM**

- **Proportion Overall Survival**

<table>
<thead>
<tr>
<th>Number At Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>112</td>
</tr>
<tr>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**SRS** | **SRS+WBRT**
---|---
Median OS | 10.4 mos | 7.4 months

---

Brown P, ASCO Plenary 2015
NO574 SRS ± WBRT 65% NSCLC

<table>
<thead>
<tr>
<th>Neurocog Decline</th>
<th>SRS</th>
<th>SRS + WBRT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>63.5%</td>
<td>91.7%</td>
<td>0.0007</td>
</tr>
<tr>
<td>6 months</td>
<td>77.8%</td>
<td>97.9%</td>
<td>0.032</td>
</tr>
</tbody>
</table>

- WBRT associated with worsening
  - Neurocognition (immediate recall, memory, verbal fluency)
  - Patient-reported outcomes such as functional well-being
- But we are probably underestimating the negative impact of SRS and new brain metastases
JLGK0901: SRS for ≤ 10 BM: Suitable alternative to SRS?

Multivariate analysis:
- Poorer survival with
  - More than 1 BM
  - Age ≥ 65 yrs
  - KPS ≤ 70
  - Male gender
  - Uncontrolled extracranial disease

Survival not associated with
- Primary tumor type
- Cumulative tumor volume

WBRT of potential little value in advanced NSCLC: QUARTZ trial

**Key results**
- No significant difference was observed in OS between the two treatment groups

![Overall survival (all patients)](image)

- Number of QALYs was also similar between the two treatment groups (43.3 vs. 41.4 days for OSC + WBRT and OSC alone, respectively)

**Conclusion**
- Whole brain radiotherapy provided no additional clinically significant benefit for patients selected for QUARTZ trial with NSCLC and brain metastases

Summary so far…

NSCLC brain metastases

- SRS alone is better than SRS+WBRT in maintaining quality of life and neurocognition.
- WBRT, as compared to SRS, does not improve quality of life or overall survival.
- SRS suitable for up to 10 brain mets, maybe more?

For patients with targetable mutations are there better alternatives?
The biology of brain metastases formation
Radiation disrupts blood brain barrier

- Activation of sphingomyelinase leads to endothelial cell damage

- Alteration of metalloproteinases, tissue inhibitors of metalloproteinases and extracellular matrix

- Disruption of BBB are seen almost immediately following radiation and may last for up to a month

Lee WH et al, IJROBP 2012
Garcia-Barros M et al, Science 2003
## NSCL brain metastases: First line chemotherapy

<table>
<thead>
<tr>
<th>Publication</th>
<th>Chemotherapy</th>
<th>ORR CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailon O et al</td>
<td>Carboplatin Pemetrexed</td>
<td>40%</td>
</tr>
<tr>
<td>Neuro Oncol 2012</td>
<td></td>
<td>39 weeks OS</td>
</tr>
<tr>
<td>(n=30 adenoca)</td>
<td></td>
<td>53% ICP</td>
</tr>
<tr>
<td>Barlesi F et al</td>
<td>Cisplatin Pemetrexed Delayed WBRT</td>
<td>42%</td>
</tr>
<tr>
<td>Ann Oncol 2011</td>
<td></td>
<td>7.4 m OS</td>
</tr>
<tr>
<td>(n= 43 NSCLC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee DH et al</td>
<td>Gemcitabine Vinorelbine vs WBRT</td>
<td>39%</td>
</tr>
<tr>
<td>Cancer 2008 (n=48)</td>
<td></td>
<td>9.1 months OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.9 months OS</td>
</tr>
</tbody>
</table>
Newly diagnosed NSCLC with synchronous brain metastases: Chemo vs WBRT

Self-reported QOL parameters (n=33)

• Global health status similarly impaired in both groups
• Cognitive function impaired in both but stable for WBRT (downward trend in chemo arm?)

Lee DH et al, Cancer 2008
WBRT (20 Gy/5 fx) with Erlotinib vs Placebo: Erlotinib has little activity in unselected patients

- Ineligible for SRS
- No need of urgent chemotherapy
- 80% were RPA II

Neurologic PFS
1.6 vs 1.6 months

Overall survival
2.9 vs 3.4 months (NS)
RTOG 0320: NSCLC Phase III
WBRT + SRS alone versus with TMZ or Erlotinib

• Closed due to poor accrual (126/381 patients)

• Median survival
  RT alone  13 m
  RT+ drug  6 m

• Time to CNS progression
  Decreased in drug arms

• Toxicity
  Increased in drug arms

Phase II gefitinib first for brain metastases EGFRmut+ Japanese patients (n=41) gefitinib → erlotinib → WBRT or SRS

- Median OS 22 months
- 88% response rate (CR+PR)
- Median time on gefitinib 10.6 months (intracranial progression most common)
- Cumulative “incidence of RT” near 100%, median delay of 17 months)
~13% had asymptomatic brain metastases at study entry of which 35% had had WBRT
PFS benefit of afatinib similar in patients with/without BM

But NS p value for BM (small numbers?)

Longer time to CNS progression in afatinib arms

Benefit of afatinib appeared higher if prior WBRT

PFS 8.2 vs 4.7 months (p=.1)  PFS 13.8 vs 8.1 months (p<.0001)
Intracranial time-to-progression of crizotinib vs chemo in ALK+ NSCLC: PROFILE 1014

- 23% had stable treated BM at baseline
- Of those BM patients, nonsignificant improvement in intracranial TTP with crizotinib (p=.064)
- Increase in brain as sole site of progression higher with crizotinib vs chemo
  - 24% vs 10% if no BM at baseline
  - 38% vs 23% if BM at baseline

BM at baseline

No BM at baseline
<table>
<thead>
<tr>
<th>Study</th>
<th>Pt number + Eligibility</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01951469 China Randomized Ph II Gefitinib + pem/cis</td>
<td>160 EGFR+, newly dx with ≥ 3 BM</td>
<td>Intracranial PFS at 3 yrs</td>
</tr>
<tr>
<td>NCT02556593 China Randomized Ph II IMRT + erlotinib vs WBRT</td>
<td>116 EGFR wild-type 4-10 BM,</td>
<td>Intracranial PFS at 2 yrs</td>
</tr>
<tr>
<td>NCT01887795 China Randomized Ph III WBRT + Erlotinib</td>
<td>224 EGFR+, ≥ 2 BM</td>
<td>Intracranial control + time to neurologic progression at 13 months</td>
</tr>
<tr>
<td>NCT02314364 USA Ph II SBRT/SRS + TKI</td>
<td>30 ALK+/EGFR+/ROS1+, oligometastases extra/intracranial (1-4 brain)</td>
<td>Freq of distant failures at 1 yr</td>
</tr>
<tr>
<td>NCT02521051 USA Ph I/II Alectinib and Bev</td>
<td>43 ALK+, ≥ 1 untreated or progressive BM</td>
<td>Determining doses + Safety/tolerability</td>
</tr>
<tr>
<td>NCT02336451 USA Ph II Ceritinib</td>
<td>125 ALK+, brain±lepto</td>
<td>Overall RR at 24 wks</td>
</tr>
</tbody>
</table>
Current practice at University of Colorado for newly dx EGFRmut+/ALK+ NSCLC with brain metastases

• SRS usually done if feasible/appropriate

• If SRS not feasible/appropriate, then TKI only

• SRS done as brain metastases progress or arise

• WBRT done in small percentage of patients
• 49 yr old M, never smoker, Stage IIIB adenoca ALK+April 2011 treated with definitive chemorads

• Jan 2014 recurrence L hilum, LLL lung, mesentery, L1, brain (9 lesions)

• Treatment to brain?
  – SRS
  – WBRT
  – SRS + WBRT
• Jan 2014 received 20 Gy to the 9 lesions with 5 isocenters
• Then started crizotinib.
• September 2014 ataxia, nystagmus, R sided paresis and R sided sensory changes
• MRI showed increase in many lesions in brain. No new lesions.
• Stable extracranial disease
• Mild improvement on steroids but symptoms recurred off steroids.
• What to do?
  Referral to neurosurgery?
  Steroids again?
  Bevacizumab?
• Received another course of steroids
• Started bevacizumab
• January 2016 2 new lesions, R parietal (enhancing) and L parietal (non-enhancing)
• Treatment?
  Continued observation?
  Change from crizotinib to another ALK inhibitor?
  SRS to one or both lesions?
  WBRT?